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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GRUN, JAMES LESLIE

ART UNIT	PAPER NUMBER
1641	7

DATE MAILED: 03/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/615,872	AREPALLY et al.
Examiner	**Art Unit**
James L. Grun, Ph.D.	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *24 Oct 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above, claim(s) *7-11 and 15-39* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6 and 12-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☒ Other: *Notice To Comply...Sequence Disclosures*

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Technology Center 1600, Group 1640, Art Unit 1641.

Applicant's election without traverse of Group I, claims 1-6 and 12-14, in Paper No. 6 is acknowledged. Claims 7-11 and 15-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

This Application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application clearly fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the sequences disclosed, e.g., in Figs. 6A and 6B, as also set forth on the "Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures" attached hereto.

Applicant is required to provide a substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, which includes each of the sequences disclosed in the specification as required by 37 CFR 1.821(c). A substitute copy of the "Sequence Listing" in computer readable form must be provided as required by 37 CFR 1.821(e). Applicant must direct the entry of "SEQ ID NO:" identifiers for every appearance of sequences in the description or claims of the patent application. Applicant must also provide a statement that the content of the paper and computer readable copies are the same and, where applicable, include no

new matter as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

The draftsperson will perform a review of the drawings filed with the specification in due course. Direct any inquiries concerning drawing review to the Drawing Review Branch at (703) 305-8404.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to and claims 1-6 and 12-14 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it

is most nearly connected, to make and/or use the invention, particularly the invention commensurate in scope with these claims.

The specification fails to provide an adequate written description of the invention and fails to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 CFR §§ 1.801-1.809. It is unclear if cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated "KKO" are known and publicly available, or can be reproducibly isolated without undue experimentation. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies necessary to practice the instant invention or filing of evidence of deposit is required. Without a publicly available deposit of the above cell lines, one of skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: the cell line; the cell lines which produce the chemically and functionally distinct antibodies claimed; and/or, the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event. For example, very different V_H chains can combine with the same V_L chain to produce antibody binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_L sequences to produce antibodies with very similar properties. These observations indicate that divergent variable region sequences, both in and out of complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical

characteristics. Therefore, it would require undue experimentation to reproduce the claimed monoclonal antibody species chemically as produced by the hybridoma designated "KKO". Moreover, one would not be able to reproduce or humanize the antibody from the instant sequence disclosure because it is entirely unclear what sequences are those of the antibody. Applicant asserts that the sequences depicted in portions of Figs. 6A and 6B are the sequences of the KKO antibody (see e.g. pages 9 and 52), yet these sequences are not those listed in Figs. 7A (see at least the C-terminal amino acid residue) or 7B, or in the sequence listing, and are not those claimed as the sequences of a functional antibody. One would not know what sequences function in the invention in view of the entirely inconsistent description of the relevant structures. Again, absent further description and guidance, it would require undue experimentation to reproduce the claimed monoclonal antibody species chemically as produced by the hybridoma designated "KKO" or any humanized derivative thereof. A suitable deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See the criteria set forth in 37 CFR §§ 1.801-1.809.

If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty, that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent and that the biological materials will be replaced should they ever become non-viable, would satisfy the deposit requirement made herein.

If the deposits have not been made under the Budapest Treaty, then in order to certify that the deposits meet the criteria set forth in 37 CFR §§ 1.801-1.809, applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposits will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) the deposits were viable at the time of deposit; and,

(e) the deposits will be replaced if they should ever become non-viable.

Further, the specification does not reasonably provide description of or enablement for any and every antibody population specific for PF4/heparin complexes other than monoclonal antibody KKO. Applicant provides guidance only for the above noted monoclonal antibody and provides no guidance as to what modifications or structure are important for the predictable function of any other monospecific antibody. As set forth above, different structures may be found on antibodies with the same specificity. Conversely, similar structure may be found on antibodies having different specificities. In the absence of any guidance other than to the use of the KKO antibodies, one would not know or be able to predict or envision what structure or modifications were important for function. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that a molecule is part of the invention and a reference to a potential method of isolating it. The molecule itself is required. Furthermore, In *The Reagents of the*

University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of molecules by only their functional activity does not provide an adequate written description of the genus. The court indicated that although applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus. Applicant is reminded that the written description provision of 35 USC 112 is severable from its enablement provision. However, in view of the guidance in the instant specification to a single species, the amount of experimentation required to determine functional structures or modifications for other usable species would also be undue. For example, as noted above, very different structures may be found on antibodies with the same specificity, and conversely, similar structure may be found on antibodies having different specificities and one would not know, given the instant guidance and absent further unguided experimentation, what variable region changes would predictably function in the invention other than those possessing both the intact V_H and V_L chains of the KKO antibody. However, as set forth above, the specification also provides insufficient description of and guidance to the functional structures of the KKO antibody. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ 2d 1027 (CAFC 1991)).

Further, with particular regard to claim 2, applicant discloses that the relevant antibodies bind to complexes of PF4 with glycosaminoglycans other than heparin (see e.g. ¶ bridging pages 23-24).

Absent further written description and guidance, one would have no assurance of obtaining an antibody with the properties as instantly claimed which binds to PF4/heparin complexes and which specifically binds to a glycosaminoglycan other than heparin in the absence of PF4. Applicant is requested to direct the examiner's attention to specific passages where support for the recited limitation can be found in the specification as filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 12-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-6 and 12-14, "the binding...with either PF4 or heparin alone" lacks antecedent basis. The acronym "PF4" should be defined at least in the independent claims as --platelet factor 4 (PF4)--.

In claim 3, "the" presence lacks antecedent basis.

In claims 4 and 13, "homology" should be --sequence identity--.

Claim 5 is vague and indefinite because it is not clear if the parenthetical recitation of "(KKO)" is intended as limitation of the invention to this antibody or if the recitation thereof is

merely exemplary of encompassed subject matter. In this claim, "the" heavy chain and "the" light chain lack antecedent basis.

Claim 14 is vague and indefinite because it is not clear if the parenthetical recitation of "(KKO)" is intended as limitation of the invention to this antibody or if the recitation thereof is merely exemplary of encompassed subject matter. In this claim, "the" heavy chain and "the" light chain lack antecedent basis.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Amiral (U.S. Pat. No. 5,466,582) in view of Blank et al (Clin. Exp. Immunol. 108: 333, 1997).

Amiral ('582) discloses detection of antibodies specific for complexes of a heparin drug with PF4 as diagnostic of heparin-induced thrombocytopenia. The reference teaches that antibodies can be detected by a competitive method using a labelled anti-antigen antibody (e.g. col. 4, line 9, col. 6, lines 10-11, and col. 8, lines 14-26), wherein the anti-antigen antibody can be monoclonal. The anti-antigen antibodies were not reduced to practice.

Blank et al teach the elicitation in mice of antibodies to heparin drug-PF4 complexes which mimic certain properties of heparin-induced thrombocytopenia patient antibodies.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited monoclonal antibodies to the heparin drug-PF4 complexes for use in the competitive assays of Amiral in view of the direct suggestion in the reference to do so. One would have had a reasonable expectation of success in the elicitation of monoclonal antibodies specific for the complexes in view of the known presence of antibodies with such specificity in patient serum samples as diagnostic of heparin-induced thrombocytopenia as taught in Amiral and in view of the elicitation of oligoclonal antibodies of such specificity in mice by Blank et al.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

A reply to a notice to comply with the sequence rules should NOT be sent to the 20231 zip code address for the United States Patent and Trademark Office.

Please direct all such replies to the United States Patent and Trademark Office via one (1) of the following:

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (703) 308-3980. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (703) 305-3399.

The phone numbers for official facsimile transmitted communications to TC 1600, Group 1640, are (703) 872-9306, or (703) 305-3014, or (703) 308-4242. Official After Final communications, only, can be facsimile transmitted to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. The above inquiries, or requests to supply missing elements from Office communications, can also be directed to the TC 1600 Customer Service Office at phone numbers (703) 308-0197 or (703) 308-0198.

James L. Grun, Ph.D.
March 20, 2002

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641